Title

Further clarifying the relationship between metformin, acute kidney injury and lactic acidosis.

Journal

Nature reviews. Nephrology, 14(1)

ISSN

1759-5061

Authors

Rhee, Connie M

Kalantar-Zadeh, Kamyar

Publication Date

2017-12-01

DOI

10.1038/nrneph.2017.174

LINK TO ORIGINAL ARTICLE
LINK TO INITIAL CORRESPONDENCE

REPLY

Further clarifying the relationship between metformin, acute kidney injury and lactic acidosis

Connie M. Rhee and Kamyar Kalantar-Zadeh

We read, with interest, the comments on our News & Views article (Diabetes mellitus: Complex interplay between metformin, AKI and lactic acidosis. *Nat. Rev. Nephrol.* **13**, 521–522 (2017))[1] by Bell, S. *et al.* (Clarifying the relationship between metformin, acute kidney injury and lactic acidosis. *Nat. Rev. Nephrol.* http://dx.doi.org/10.1038/nrneph.2017.172 (2017))[2], and we would like to respond to their important points.

First, we concur that metformin should be temporarily discontinued in patients with conditions that predispose to acute kidney injury (AKI). Although this is not consistently recommended by regulatory bodies and guidelines[3,4], the studies by Connelly *et al.* and Bell *et al.* provide much-needed evidence for the potential toxicity of metformin in this context[5,6].

Second, we concur that crude incidence rates of lactic acidosis may differ across studies that have heterogeneous patient populations. However, large observational studies using clinical databases may not accurately estimate the real-world incidence of metformin-associated lactic acidosis (MALA), particularly if ascertained using blood lactate levels ordered at the discretion of clinicians (instead of using a strict protocol for measurement among all study participants) or by diagnostic codes, in several ways[4,7,8]: first, eligibility criteria that requires patients to have one lactate measurement for inclusion may miss patients with elevated levels of lactate that aren't measured; second, metformin users may undergo more frequent lactate measurement than non-users, overestimating the risk of MALA; and third, the risk of MALA could conversely be underestimated owing to confounding by indication, as metformin users appeared to be healthier than non-users in both the Connelly *et al.* and Bell *et al.* studies[5,6].

Third, regarding the absence of a new-user design, we agree that the ability of the study by Bell *et al.* to follow the majority of patients over an extended period with prescribing data from all pharmacies in the Tayside region is a major strength that mitigates potential survivor bias.

Fourth, we concur that the findings of 'ever' versus 'never' metformin use and risk of AKI may potentially be explained by confounding factors (that is, metformin as a marker for coexisting comorbidities). However, using the summary of table 2 in the original study (of patient characteristics stratified by time-updated metformin exposure status) as a gauge for the distribution of characteristics among metformin 'ever' versus 'never' users, there appears to be a tendency towards metformin prescription among healthier patients.

Finally, we acknowledge that there is widespread debate regarding the use of metformin in patients with chronic kidney disease (CKD), including the precise threshold at which this medication should be restricted[4,7–12]. However, patients with CKD have a greater, often unanticipated, susceptibility to AKI and a lower underlying reserve of renal function when AKI occurs[8,13]. Furthermore, a large proportion of patients with CKD have AKI-predisposing conditions (for example, infection and/or sepsis, congestive heart failure and myocardial infarction) that further elevate their risk of MALA[14]. It is worth mentioning that one study, cited by the investigators in their correspondence, showed that there was a trend towards higher risk of acidosis and serious infection among metformin users with an estimated glomerular filtration rate (eGFR) <45 ml/min/1.73 m^2 (REFS 3,15) and that another study[16] excluded patients with CKD (serum creatinine ≥1.5 mg/dl) or serious medical illness. Moreover, the high mortality rate from MALA and the multitude of alternative anti-diabetic pharmacotherapies available calls into question whether a small risk of metformin justifies its benefit. Although a recent rigorous systematic review concluded that limited evidence suggests that metformin does not substantially affect lactate levels when eGFR is >30 ml/min/1.73 m^2 and that a consistent link between metformin and lactic acidosis was not observed across available evidence[7], further studies, including randomized controlled trials that test the tolerability and effectiveness of metformin in CKD and the precise eGFR threshold above which metformin is safe, are urgently needed.

Connie M. Rhee is at the Harold Simmons Center for Chronic Disease Research and Epidemiology, University of California Irvine School of Medicine, Orange, California 92868, USA.

Kamyar Kalantar-Zadeh is at the Harold Simmons Center for Chronic Disease Research and Epidemiology, University of California Irvine School of Medicine, Orange, California 92868, USA; and at the Tibor Rubin Veterans Affairs Medical Center, Long Beach, California 90822, USA.

Correspondence to K.K.-Z.
kkz@uci.edu

doi:10.1038/nrneph.2017.174
Published online 13 Dec 2017

1. Rhee, C. M. & Kalantar-Zadeh, K. Diabetes mellitus: complex interplay between metformin, AKI and lactic acidosis. *Nat. Rev. Nephrol.* **13**, 521–522 (2017).
2. Bell, S., Soto-Pedre, E., Connelly, P., Livingstone, S. & Pearson, E. Clarifying the relationship between metformin, acute kidney injury and lactic acidosis. *Nat. Rev. Nephrol.* http://dx.doi.org/10.1038/nrneph.2017.172 (2017).
3. U.S. Food and Drug Administration. Drug safety and availability. *U.S. Food and Drug Administration* http://www.fda.gov/Drugs/DrugSafety (2017).
4. Rhee, C. M., Kovesdy, C. P. & Kalantar-Zadeh, K. Risks of metformin in type 2 diabetes and chronic kidney disease: lessons learned from Taiwanese data. *Nephron* **135**, 147–153 (2017).
5. Bell, S. *et al.* Risk of acute kidney injury and survival in patients treated with metformin: an observational cohort study. *BMC Nephrol.* **18**, 163 (2017).
6. Connelly, P. J. *et al.* Acute kidney injury, plasma lactate concentrations and lactic acidosis in metformin users: a GoDarts study. *Diabetes Obes. Metab.* **19**, 1579–1586 (2017).
7. Inzucchi, S. E., Lipska, K. J., Mayo, H., Bailey, C. J. & McGuire, D. K. Metformin in patients with type 2 diabetes and kidney disease: a systematic review. *JAMA* **312**, 2668–2675 (2014).
8. Rhee, C. M. & Kalantar-Zadeh, K. Restricting metformin in CKD: continued caution warranted. *Am. J. Kidney Dis.* **66**, 1101–1102 (2015).
9. Bakris, G. L. & Molitch, M. E. Should restrictions be relaxed for metformin use in chronic kidney disease? Yes, they should be relaxed! What's the fuss? *Diabetes Care* **39**, 1287–1291 (2016).
10. Kalantar-Zadeh, K. & Kovesdy, C. P. Should restrictions be relaxed for metformin use in chronic kidney disease? No, we should never again compromise safety! *Diabetes Care* **39**, 1281–1286 (2016).
11. Kalantar-Zadeh, K. & Rhee, C. M. Metformin in chronic kidney disease: more harm than help? *Lancet Diabetes Endocrinol.* **3**, 579–581 (2015).
12. Stanton, R. C. Metformin use in type 2 diabetes mellitus With CKD: is it time to liberalize dosing recommendations? *Am. J. Kidney Dis.* **66**, 193–195 (2015).
13. Kalantar-Zadeh, K., Uppot, R. N. & Lewandrowski, K. B. Case records of the Massachusetts General Hospital. Case 23–2013. A 54-year-old woman with abdominal pain, vomiting, and confusion. *N. Engl. J. Med.* **369**, 374–382 (2013).
14. United States Renal Data System. *USRDS 2017 Annual Data Report: Atlas of Chronic Kidney DIsease and End-Stage Renal Disease in the United States* (National Institutes of Health, 2017).
15. Ekstrom, N. *et al.* Effectiveness and safety of metformin in 51 675 patients with type 2 diabetes and different levels of renal function: a cohort study from the Swedish National Diabetes Register. *BMJ Open* **2**, e001076 (2012).
16. Roumie, C. L. *et al.* Comparative effectiveness of sulfonylurea and metformin monotherapy on cardiovascular events in type 2 diabetes mellitus: a cohort study. *Ann. Intern. Med.* **157**, 601–610 (2012).

Competing interests statement
The authors declare no competing interests.